论著·临床医学

单次静脉注射小剂量瑞马唑仑降低剖宫产术后寒战风险并促进术后恢复:一项随机双盲对照试验

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[**摘要**] **目的** 腰硬联合麻醉下剖宫产术后寒战发生率高,会导致产妇不适、增加氧耗、干扰生命体征监测,甚至引发不良心血管及呼吸事件。瑞马唑仑(新型超短效苯二氮䓬类药物)在全身麻醉中可降低术后寒战发生率,本研究旨在评估瑞马唑仑对腰硬联合麻醉下剖宫产术后寒战的预防效果及对产妇术后恢复质量的影响。**方法** 采用前瞻性随机双盲安慰剂对照研究设计方案,选取2025年6—12月在西安交通大学第一附属医院榆林医院行择期腰硬联合麻醉下剖宫产术的单胎足月产妇140例(年龄24~40岁,ASA Ⅱ级,BMI≤35 kg/m^2),随机分配至瑞马唑仑(Remimazolam,胎儿娩出夹闭脐带后静脉注射瑞马唑仑0.2 mg/kg)组和对照(Control,给予等容量生理盐水)组(n=70)。采用床旁寒战评估量表BSAS评估2组椎管内麻醉后90 min内中重度寒战发生率,术后1、2 d恢复质量(包括情绪状态、心理支持、身体舒适度、身体独立性和疼痛5个维度量表)、给药后90 min内警觉/镇静评估(OAA/S)评分及术中不良反应(低血压、心动过缓、恶心、呕吐、头晕)等指标。**结果** 2组产妇年龄、体质量、孕周、初产妇比率、麻醉阻滞平面、术中失血量及手术时长等基线资料差异均无统计学意义(P>0.05)。①主要结局事件:Remimazolam组中重度寒战总发生率为27.1%(19/70),显著低于Control组的55.7%(39/70,P<0.001);与Control组相比,Remimazolam组发生中重度寒战的风险降低62%(HR=0.38,95%CI:0.22~0.67,P=0.000 4);0~30 min时段Remimazolam组中重度寒战发生率(10.0%)显著低于Control组(25.7%,P=0.027)。②次要结局事件:术后1 d QoR-15总分Remimazolam组为126(124,128)分,显著高于Control组的116(115,118)分(P<0.001);术后2 d Remimazolam组为141(140,143)分,显著高于Control组的133(130,135)分(P<0.001)。其中Remimazolam组在情绪状态、心理支持、身体舒适度3个维度评分均高于Control组(均P<0.001),2组在身体独立性和疼痛维度评分差异无统计学意义(P>0.05)。Remimazolam组给药后15 min OAA/S评分为5(4,5)分,低于Control组的5(5,5)分(P=0.004),30 min后恢复至对照组水平(P>0.05)。2组心动过缓、低血压、恶心、呕吐及头晕等不良反应发生率差异均无统计学意义(均P>0.05)。**结论** 腰硬联合麻醉下剖宫产术中胎儿娩出后单次静脉注射0.2 mg/kg瑞马唑仑,可使术后中重度寒战风险降低62%,同时可显著改善产妇术后1、2 d的恢复质量(尤其在情绪状态、心理支持和身体舒适度维度),且仅产生轻度、可逆的术中镇静作用,不增加不良反应风险。

[**关键词**] 瑞马唑仑;寒战;剖宫产术;脊髓麻醉;功能恢复

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Single-dose intravenous remimazolam reduces risk of post-cesarean shivering and promotes postoperative recovery: a randomized double-blind controlled trial

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[**Abstract**] Objective Post-cesarean shivering under combined spinal-epidural anesthesia (CSEA) is highly prevalent, which can cause to maternal discomfort, increase oxygen consumption, interfere with vital sign monitoring, and potentially lead to adverse cardiovascular and respiratory events. Remimazolam, a novel ultrashort-acting benzodiazepine, has been shown to reduce postoperative shivering in general anesthesia. This study aims to evaluate the prophylactic effect of remimazolam on post-cesarean shivering under CSEA and its impact on maternal recovery quality. Methods A prospective randomized double-blind placebo-controlled trial was conducted on 140 singleton full-term parturients (aged 24–40 years, ASA physical status II, BMI ≤35 kg/m^2) undergoing elective cesarean section under CSEA in our hospital from June to December 2025. They were randomly assigned to a remimazolam group (Group Remimazolam, receiving a single intravenous injection of remimazolam 0.2 mg/kg immediately after delivery and umbilical cord clamping, n=70) and a control group (Group Control, n=70, receiving an equal volume of normal saline). The incidence of moderate-to-severe shivering within 90 min after neuraxial anesthesia [assessed using the Bedside Shivering Assessment Scale (BSAS)]. quality of recovery on postoperative days 1 and 2 [measured by the 15-item Quality of Recovery (QoR-15) scale, covering 5 dimensions: emotional state, psychological support, physical comfort, physical independence, and pain], Observer′s Assessment of Alertness/Sedation (OAA/S) scores within 90 min after drug administration, and intraoperative adverse reactions (hypotension, bradycardia, nausea. vomiting and dizziness) were compared between the 2 groups. Results There were no statistically significant differences in baseline characteristics between the 2 groups, including age, body weight, gestational age, primipara ratio, anesthetic block level, intraoperative blood loss, or operative duration (all P>0.05). ① For the primary outcome, the overall incidence of moderate-to-severe shivering in Group Remimazolam was 27.1% (19/70), significantly lower than that in Group Control [55.7% (39/70), P<0.001]. Remimazolam reduced the risk of moderate-to-severe shivering by 62% compared with the risk in the Group Control (HR=0.38, 95%CI: 0.22 to 0.67, P=0.000 4). During the 0–30 min period, the incidence of moderate-to-severe shivering was significantly lower in Group Remimazolam than in Group Control (10.0% *vs* 25.7%, P=0.027). ② For secondary outcomes, the QoR-15 total score on postoperative day 1 was 126 (124, 128) in Group Remimazolam, which was significantly higher than that in the Control group [116 (115, 118), P<0.001]; on postoperative day 2, the Remimazolam group scored 141 (140, 143), which was significantly higher than that in the Control group [133 (130, 135), P<0.001]. Group Remimazolam showed significantly higher scores in the dimensions of emotional state, psychological support, and physical comfort (all P<0.001), whereas there were no statistically significant differences between the 2 groups in the dimensions of physical independence or pain (P>0.05). The OAA/S score at 15 min after drug administration in the Remimazolam group was 5(4, 5), which was lower than that in the Control group [5 (5, 5), P=0.004], and returned to the level of the control group after 30 min (P>0.05). No significant differences were observed in the incidence of bradycardia, hypotension, nausea, vomiting or dizzines between the 2 groups (all P>0.05). Conclusion A single intravenous dose of 0.2 mg/kg remimazolam administered immediately after delivery during cesarean section under CSEA can significantly reduce the risk of moderate-to-severe post-cesarean shivering by 62%, also improve the quality of maternal recovery on postoperative days 1 and 2 (particularly in the dimensions of emotional state, psychological support, and physical comfort). The regimen produces only mild, reversible intraoperative sedation without increasing the risk of adverse reactions.

[**Key words**] remimazolam; shivering; cesarean section; anesthesia, spinal; functional recovery

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在剖宫产手术中,腰硬联合麻醉(combined spinal and epidural anesthesia, CSEA)是临床常用的麻醉方式,术后寒战是其常见的并发症之一,发生率高达55%[1-3]。寒战不仅会导致产妇出现明显不适,还会干扰生命体征的监测,增加产妇的氧耗,进而可能带来心血管及呼吸系统不良影响[4]。近年来,国内外研究发现多种药物对术后寒战具有一定的预防和防治效果,如昂丹司琼、曲马多、地佐辛、芬太尼、舒芬太尼、右美托咪定、艾司氯胺酮等[5-6]。瑞马唑仑作为一种新型的超短效苯二氮䓬类药物,自2020年在中国大陆上市以来,因其起效迅速、作用时间短、代谢速率快以及不良反应轻等优点,在临床麻醉领域得到了广泛关注与应用。有研究表明小剂量瑞马唑仑(0.2 mg/kg)对机体呼吸及循环无明显抑制作用[7-9]。另有报道指出,小剂量瑞马唑仑可有效预防全身麻醉术中低体温及术后寒战[10]。目前,临床中尚缺乏关于小剂量瑞马唑仑对腰硬联合麻醉下剖宫产术后寒战及术后恢复质量的影响的报道。因此,本研究选取我院择期行剖宫产手术的患者作为研究对象,旨在评估静脉注射0.2 mg/kg瑞马唑仑对剖宫产术患者椎管内麻醉后寒战的预防效果,同时评价其对产妇术后恢复质量的影响。

1 资料与方法

1.1 研究对象

本研究采用前瞻性随机双盲安慰剂对照研究设计方案,已通过西安交通大学第一附属医院榆林医院伦理委员会审批(伦理号:2025-005)与中国临床试验注册中心注册(注册号:ChiCTR2500104429)。所有产妇均签署知情同意书。依据相关文献及本中心既往数据,对照组腰硬联合麻醉下剖宫产术后寒战发生率约为65.7%,假设瑞马唑仑可将其降至42.9%,预期两组率差为22.8%。设定双侧检验水准α=0.05,检验效能1-β=0.90,采用两独立样本率比较公式估算样本量,计算得每组需65例。考虑10%脱落率,最终确定每组纳入70例,两组共140例。选择2025年6月至2025年12月在西安交通大学第一附属医院榆林医院麻醉科进行择期CSEA下剖宫产术的140例单胎妊娠产妇为研究对象。纳入标准:①年龄24~40岁;②ASA分级Ⅱ级;③BMI≤35 kg/m^2;④足月妊娠且是住院病人。排除标准:①存在腰硬联合麻醉禁忌症;②对本研究所用药物过敏;③体温≥38 ℃或≤36 ℃,或WBC水平<4×10^9/L或>10×10^9/L;④合并严重心、肺、肾等重要脏器疾病或合并严重妊娠期并发症;⑤精神异常;⑥手术开始前麻醉平面低于T_8或高于T_4;⑦联合使用静脉全身麻醉,硬膜外出血或穿破蛛网膜;⑧手术时间超过90 min或术中失血量≥1 000 mL或术中缩宫素用量大于>60 U;⑨产妇要求退出研究。采用随机数字表法将产妇分为2组(n=70):瑞马唑仑组(Remimazolam组)和对照组(Control组),使用按顺序编号的不透明的密封信封对组别的分配进行隐藏。

1.2 麻醉方法

所有产妇术前按常规禁食禁饮,入室后常规监测ECG、HR、BP、SpO_2,鼻导管吸氧2 L/min。维持室温24 ℃~25 ℃,湿度55%~65%。开放左上肢静脉通道,快速输注预热至37 ℃的醋酸钠林格注射液250 mL。选择L_2-L_3或L_3-L_4间隙行硬膜外穿刺,当硬膜外穿刺针刺破黄韧带时有落空感,同时注射空气阻力消失,回抽无脑脊液流出,确认穿刺成功后,通过穿刺针向蛛网膜下腔注入0.66%罗哌卡因2.0~2.5 mL,拔出穿刺针,然后向头侧置入软头金属钢丝硬膜外导管3~4 cm备用,穿刺完成后产妇取仰卧并向左倾斜15°,调整手术床体位,麻醉平面控制在T_{6-8}。若术中镇痛不足,通过硬膜外导管注入2%利多卡因5 mL。胎儿娩出后,产妇Remimazolam组静脉输注瑞马唑仑0.2 mg/kg,产妇Control组给予等容量生理盐水。若产妇出现仰卧位低血压综合征(SBP<90 mmHg),静脉注射去氧肾上腺素40~60 μg或麻黄碱6 mg;若HR<50次/分,静脉注射阿托品0.5 mg。两组产妇术毕均行患者静脉自控镇痛(patient-controlled intravenous analgesia,PCIA),镇痛泵配方:舒芬太尼2 μg/kg+帕洛诺司琼0.15 mg,用生理盐水稀释至100 mL,镇痛泵背景输注速率设置为2 mL/h,单次按压剂量2 mL,锁定时间15 min。

1.3 双盲实施流程

①药物的配制与包装:瑞马唑仑注射液与0.9%氯化钠注射液在颜色、外观、包装容器上完全一致。研究药物由不参与临床评估、不参与结局测量、不参与统计分析的药剂科专职药师于手术前统一配制。配制完成后,所有注射器外观完全一致,仅以按顺序编号的标签(如研究药物-001至研究药物-140)进行标识,无任何提示药物成分的信息。

②随机化与分配隐藏:采用计算机生成的区组随机化序列,将140例受试者按1∶1比例分配至Remimazolam组或Control组。随机序列由独立统计师生成并密封入按顺序编号的不透明信封中。信封由专职药师保管,仅在产妇入组后按顺序拆封,以确定该产妇应使用的研究药物编号。分配序列对受试者、结局评估者及统计分析人员均严格保密。当日值

班给药麻醉医师因承担用药安全职责,在拆封信封给药时知晓分组情况,但不参与任何结局指标的评估。

③给药过程:由当日值班但不参与结局评估的麻醉医师根据信封指示的研究药物编号,取用对应注射器并于胎儿娩出后立即开始静脉输注。给药者知晓分组情况(因需承担用药安全职责),但不参与任何结局指标的评估。给药过程中,注射泵外观以不透明布套覆盖,避免受试者及手术室其他人员识别药物类型。

1.4 观察指标

所有结局指标均由经过统一培训的独立评估人员进行测量,该评估人员不参与受试者的麻醉管理、不参与研究药物的配制与给药,且在研究全过程中对分组情况保持盲态(即不知晓受试者被分配至Remimazolam组或Control组)。

1.4.1 采用QoR-15量表评估术后恢复质量 使用QoR-15评分评估两组产妇术后1 d、2 d的恢复情况。涵盖5个维度,包括15个问题:①身体舒适度(5个问题);②情绪状态(4个问题);③身体独立性(2个问题);④心理状态(2个问题);⑤疼痛(2个问题)。每个问题采用10分量表评分,范围从0到10分。患者的总分是所有问题得分之和,总分范围为0(最差恢复质量)到150(最佳恢复质量)。

1.4.2 采用床旁寒战评估量表(BSAS)评估寒战发生率及严重程度 麻醉后30 min内每5 min进行评估,30 min后每10 min进行评估,总观察时间为90 min,记录首次观察到的寒战时间点。采用床旁寒战评估量表(bedside shivering assessment scale,BSAS)评估寒战的严重程度,将寒战评定为①0级:无寒战,咬肌、颈部、胸壁触诊未发现寒战;②1级:轻度寒战,寒战仅局限于颈部和胸部;③2级:中度寒战,涉及上肢粗大运动(除颈部和胸部外);④3级:重度寒战,寒战涉及躯干、上肢和下肢的粗大运动。

1.4.3 采用警觉/镇静评估(OAA/S)评分评估术中镇静深度 记录静脉给药后90 min内(每隔15 min评估)2组产妇各自的OAA/S评分。具体评分标准如下:①5分:清醒状态,患者对正常语调的呼名反应迅速,言语和面部表情正常,眼睛无下垂。②4分:轻度镇静,患者对正常语调的呼名反应迟钝,言语稍缓慢或含糊,面部表情轻微放松,眼睛有轻度下垂。③3分:中度镇静,患者仅对大声呼名有反应,言语明显迟钝或缓慢,面部表情明显放松,眼睛明显下垂。④2分:深度镇静,患者仅对轻推或摇动有反应,言语几乎无法分辨,面部表情和眼睛反应减弱。⑤1分:深度睡眠或无意识,患者对轻推或摇动无反应。

1.4.4 术中不良反应监测 比较两组产妇术中不良反应(低血压、呼吸困难、心动过缓、恶心、呕吐、头晕)的发生情况。盲法保障措施:①研究方案明确规定,所有参与结局评估的人员在签署保密协议后方可入组,且在整个研究期间禁止查阅随机化列表或与其他研究团队成员讨论分组信息。②手术室记录单、病历及随访表格中均不出现“瑞马唑仑组”或“对照组”字样,仅以受试者编号标识。③QoR-15问卷由评估人员B在安静的病房环境中单独指导产妇填写,确保不受其他人员干扰。④若出现严重不良事件需紧急揭盲时,由DSMB执行个别揭盲,评估人员保持盲态不变。

1.5 统计学分析

采用SPSS 26.0软件进行统计学分析。正态分布的计量资料以$\bar{x}\pm s$表示,组间比较采用独立样本t检验;非正态分布的计量资料以$M(P_{25},P_{75})$表示,组间比较采用非参数数据的秩和检验。计数资料以频次(%)表示,比较采用χ^2检验。使用Kaplan-Meier曲线评估中重度寒战发生与时间的关系。对于两组产妇术后1 d、2 d QoR-15评分比较,采用Bonferroni法进行多重比较校正,控制Ⅰ类错误风险。P<0.05表示差异有统计学意义。

2 结果

2.1 两组产妇基线资料均衡,具有可比性

两组产妇年龄、体质量、孕周、初产妇比率、胸神经感觉阻滞平面、术中失血量以及手术时长比较,差异均无统计学意义,见表1。

2.2 瑞马唑仑显著降低椎管内麻醉后中重度寒战发生率及发生风险

将麻醉后90 min内的中重度寒战发生情况按0~15 min、15~30 min、30~45 min、45~60 min、60~75 min、75~90 min进行分层分析,结果见表2。发现瑞马唑仑的抗寒战效果与其药代动力学特征高度吻合(起效1~2 min,达峰3~5 min,半衰期30~60 min)。椎管内麻醉后90 min内,中重度寒战的总发生率[27.1%(19例)]低于Control组[55.7%(39例),P<0.05]。与Control组比较,Remimazolam组椎管内麻醉后90 min内发生中重度寒战的风险降低,风险比(hazard ratio,HR)为0.38,95% CI:0.22~0.67,P=0.000 4。2组产妇椎管内麻醉后90 min内中重度寒战与时间的关系,见图1。

2.3 瑞马唑仑给药后15 min OAA/S评分显著降低

Remimazolam组椎管内麻醉后15 min OAA/S评

表1 2组产妇基本临床信息比较[n=70, $\bar{x}\pm s$, $M(P_{25},P_{75})$]

Table 1 Comparison of basic clinical characteristics between the 2 groups of parturients [n=70, $\bar{x}\pm s$, $M(P_{25},P_{75})$]

Items	Group Control	Group Remimazolam	$t/\chi^2/Z$	P
Age/years	33.4±3.9	32.7±3.8	1.13	0.26
Height/cm	160.3±5.5	161±5.0	0.84	0.40
Weight/kg	74.9±10.1	74.9±8.1	0.20	0.84
Gestational age/weeks	38.3±1.6	38.3±1.3	0.12	0.91
Primiparity rate/n(%)	42.0(60.0)	40.0(57.1)	0.12	0.73
Body temperature/℃	36.4±0.2	36.3±0.2	1.17	0.24
Sensory block level	T_6(T_6, T_7)	T_6(T_6, T_7)	1.45	1.47
Intraoperative blood loss/mL	312.9±61.2	310.0±68.4	0.13	0.90
Duration of surgery/min	46.1±7.5	47.0±7.2	0.63	0.53

表2 2组产妇椎管内麻醉后不同时段中重度寒战发生情况比较[n=70, 例(%)]

Table 2 Comparison of the incidence of moderate-to-severe shivering at different time periods after intrathecal anesthesia between the 2 groups [n=70, n (%)]

Time	Group Control	Group Remimazolam	χ^2	P
0—15 min	9(12.9)	3(4.3)	2.28	0.13
15—30 min	9(12.9)	4(5.7)	1.36	0.24
30—45 min	12(17.1)	4(5.7)	3.46	0.06
45—60 min	8(11.4)	8(11.4)	0	1.00
60—75 min	0	0	—	—
75—90 min	1(1.4)	0	0	1.00

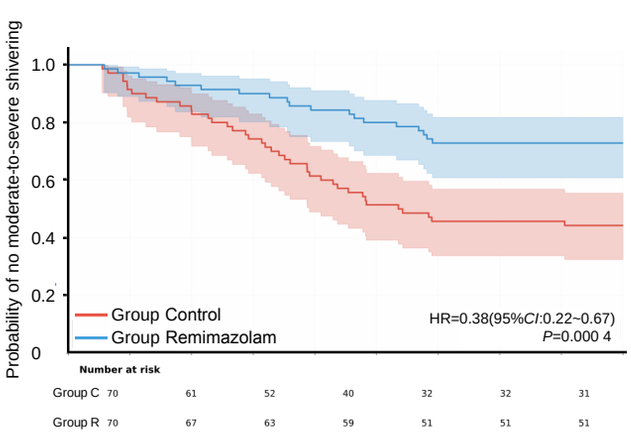


图1 2组产妇椎管内麻醉后90 min内中重度寒战与时间的关系

Figure 1 Relationship between moderate-to-severe shivering and time within 90 min after intrathecal anesthesia in the 2 groups

分低于Control组(P<0.05);两组产妇椎管内麻醉后30、45、60、75、90 min OAA/S评分差异均无统计学意义(P>0.05),见表3。

2.4 瑞马唑仑不增加术中不良反应发生率

分别记录2组产妇术中不良反应,包括心动过缓、低血压、呼吸困难、恶心、呕吐及头晕,统计分析显示以上不良反应的发生率均无统计学意义(P>0.05),见表4。

2.5 瑞马唑仑显著提高产妇术后1 d、2 d QoR-15评分

Remimazolam组术后1 d、2 d QoR-15评分在情绪状态、心理支持、身体舒适度3个维度以及总分高于Control组,见表5。

3 讨论

寒战是机体应对低温的一种重要生理反应,其机制复杂且受多种因素影响。寒战作为剖宫产手术椎管内麻醉常见的并发症,其发生给产妇带来心理和生理的巨大阴影[5, 11-12]。有些体温正常的产妇在进入手术室和麻醉后,随即出现不可控制的颤抖样寒战,可能与宫缩痛、情绪剧烈波动以及阻滞平面较高有关[13-14]。因此本研究涵盖了尽可能多的影响因素,包括是否为初产妇、胸神经感觉阻滞平面、手术时长、术

表3 2组产妇椎管内麻醉后90 min内OAA/S评分比较[n=70,分,$M(P_{25},P_{75})$]

Table 3 Comparison of OAA/S scores within 90 min after intrathecal anesthesia between the 2 groups [n=70, score, $M(P_{25},P_{75})$]

Group	Post-intrathecal anesthesia/min					
	15	30	45	60	75	90
Control	5(5,5)	5(5,5)	5(5,5)	5(5,5)	5(5,5)	5(5,5)
Remimazolam	5(4,5)[a]	5(5,5)	5(5,5)	5(5,5)	5(5,5)	5(5,5)
Z	2.98	1.76	1.76	1.76	1.76	1.76
P	0.004	0.083	0.083	0.083	0.083	0.083

OAA/S: Observer's assessment of alertness/sedation. a: P<0.05, compared with Group Control

表4 2组产妇术中不良反应发生情况比较[n=70,例(%)]

Table 4 Comparison of the incidence of intraoperative adverse events between the 2 groups [n=70, n (%)]

Group	n	Bradycardia	Hypotension	Dyspnea	Nausea	Vomiting	Dizziness
Control	70	0	14(20.0)	0	21(30.0)	6(8.6)	0
Remimazolam	70	0	15(21.4)	0	20(28.6)	6(8.6)	5(7.1)
χ^2		—	0	—	0	0	—
P		1.0	1.00	1.00	1.00	1.00	0.058

表5 2组产妇术后24、48 h QoR-15评分比较[n=70,分,$M(P_{25},P_{75})$]

Table 5 Comparison of QoR-15 scores at 24 h and 48 h after surgery between the 2 groups [n=70, score, $M(P_{25},P_{75})$]

Items	24 h after surgery				48 h after surgery			
	Group Control	Group Remimazolam	Z	P	Group Control	Group Remimazolam	Z	P
Emotional state (40)	31(30,32)	33(32,34)[a]	13.36	<0.001	34(33,35)	38(38,39)[a]	47.51	<0.001
Psychological support (20)	14(13,15)	17(16,18)[a]	36.46	<0.001	17(16,18)	18(18,19)[a]	8.74	<0.001
Physical comfort (50)	39(38,40)	43(42,44)[a]	33.40	<0.001	44(43,45)	48(47,48)[a]	20.28	<0.001
independence (20)	17(16,18)	17(16,18)	1.18	0.24	19(19,20)	19(18,20)	0.22	0.83
Pain (20)	16(15,16)	16(15,16)	0.58	0.56	18(18,19)	18(17,19)	0.62	0.54
Total score (150)	116(115,118)	126(124,128)[a]	93.69	<0.001	133(130,135)	141(140,143)[a]	48.30	<0.001

QoR-15: 15-item Quality of Recovery scale. a: P<0.05, compared with Group Control

中失血量、肝肾功能指标以及血糖水平。并且术中通过严格控制手术室温度、输入液体加温,排除混杂因素的影响。

3.1 单次小剂量瑞马唑仑显著降低剖宫产术后寒战发风险

剖宫产术中寒战的发生高峰期通常在胎儿娩出后30分钟内[15]。本研究选择在胎儿娩出夹闭脐带后立即注射瑞马唑仑0.2 mg/kg。结果显示,Remimazolam组中重度寒战发生率为27.1%,显著低于Control组的55.7%(P=0.001)。与Control组相比,Remimazolam组发生中重度寒战的风险降低,HR=0.38(95%CI:0.22~0.67),P=0.000 4。这一结果表明,静脉注射小剂量瑞马唑仑可显著降低腰硬联合麻醉下剖宫产产妇术后寒战发生率,且作用主要体现在寒战发生高峰期(0~30 min)。

瑞马唑仑起效时间1~2 min,3~5 min达峰值,持续时间15~30 min。本研究选择在胎儿娩出夹闭脐带后立即给予瑞马唑仑0.2 mg/kg,药物在0~30 min内达到有效血药浓度,因此在此阶段显示出显著的抗寒战效果。时间分层分析显示,0~30 min时段Remimazolam组中重度寒战发生率(10.0%)显著低于Control组(25.7%,P=0.027),进一步验证了瑞马唑仑的药代动力学特点与其抗寒战时效的高度吻合。30~60 min时段,随着药物代谢,血药浓度逐渐下降,抗寒战效果减弱,但仍可见一定的保护作用(17.1% *vs* 28.6%),提示可能存在残留效应。60~90 min时段,两组寒战发生率均极低,未观察到延迟性反跳现象,说明瑞马唑仑不会导致停药后寒战发生率反跳性增高。

目前关于瑞马唑仑抗寒战机制的研究较少,其作用可能源于以下药理特性:作为苯二氮䓬类药物,瑞马唑仑通过增强γ-氨基丁酸(gamma-aminobutyric acid,GABA)A型受体活性抑制中枢神经系统兴奋性,

降低寒战相关神经传导阈值[16],减少椎管内麻醉引发的寒战反射触发[17];其血流动力学稳定的特性可减轻低血压及血管扩张引起的体温下降,间接抑制寒战[18];其起效迅速、半衰期短,小剂量即可精准调控镇静深度,避免过度抑制中枢神经系统[16],既可控制寒战又可减少药物蓄积对母婴的潜在风险。值得注意的是,Cho等[19]报道瑞马唑仑在全凭静脉麻醉时术中低体温发生率高于吸入麻醉,提示其对体温调节的影响可能因麻醉方式不同而异,相关机制尚待深入研究。值得关注的是,现有临床研究对瑞马唑仑在围术期寒战预防中的效果呈现出一定的差异性。Lee C等[20]在腹腔镜妇科手术全身麻醉患者中进行的一项前瞻性随机对照试验显示,与七氟醚维持麻醉相比,瑞马唑仑全凭静脉麻醉组PACU寒战发生率显著降低,且寒战严重程度更轻,提示瑞马唑仑在全身麻醉条件下具有明确的抗寒战优势。然而,Lee J等在内镜鼻窦手术中发现,瑞马唑仑全凭静脉麻醉组术中低体温发生率反而高于吸入麻醉组,提示瑞马唑仑对体温调节的影响可能因手术类型、麻醉方式及给药时机的不同而存在差异[21]。这些研究结果的异质性强调在不同手术和麻醉背景下评估瑞马唑仑抗寒战效果的必要性。

与现有常用于预防剖宫产术后寒战的药物相比,瑞马唑仑在药代动力学特征、安全性及术后恢复质量方面展现出独特的综合优势。右美托咪定作为高选择性α_2肾上腺素能受体激动剂,虽能有效降低寒战发生率,但静脉给药后可引起明显的心动过缓和低血压,且其镇静作用持续时间较长,可能延迟产妇术后早期清醒和母婴接触[6,22]。曲马多通过阿片及单胺能机制发挥抗寒战作用,但恶心呕吐等不良反应发生率较高,且缺乏特异性拮抗剂[23-24]。昂丹司琼对寒战的预防效果尚存争议,现有研究结果显示其降低寒战发生率的效果有限[11,25]。相比之下,瑞马唑仑作为超短效苯二氮䓬类药物,起效时间仅1~2 min,半衰期约30~60 min,且可被氟马西尼特异性拮抗[7,23],在胎儿娩出后即刻给药即可精准覆盖寒战发生高峰期(0~30 min),同时不影响术后早期恢复和母婴接触。本研究中瑞马唑仑组术后QoR-15评分显著高于对照组,而右美托咪定和曲马多的相关研究多未报告术后恢复质量的全面评估。因此,在CSEA剖宫产这一特定场景中,瑞马唑仑凭借其快速可控的药代动力学、温和的血流动力学影响、可拮抗的安全性以及改善术后恢复质量的双重获益,显示出较现有药物更为理想的综合应用前景。

3.2 瑞马唑仑改善产妇术后早期恢复质量,获益主要体现在情绪与舒适度维度

本研究选择QoR-15量表进行评估术后恢复情况。结果显示,Remimazolam组术后1 d QoR-15中位评分126分,显著高于Control组的116分;术后2 d中位评分为141分,显著高于Control组的133分,获益主要体现在情绪状态、心理支持、身体舒适度3个维度,表明静脉注射小剂量瑞马唑仑可显著改善产妇术后早期恢复质量。然而,2组产妇在身体独立性和疼痛方面评分差异均无统计学意义,可能是术后镇痛方案比较满意。既往关于瑞马唑仑与术后恢复质量的研究主要集中在全身麻醉手术中,且结果尚不完全一致。在泌尿外科手术中比较了瑞马唑仑与丙泊酚的全身麻醉效果,发现瑞马唑仑组术后第1天QoR-15评分反而低于丙泊酚组,差异具有临床意义;但至术后第3天差异消失[26]。然而,在颈椎前路椎间盘切除融合术中的随机对照试验显示,瑞马唑仑组与七氟醚组术后第1天QoR-15总分无统计学差异,但瑞马唑仑组在心理支持维度和术后恶心呕吐方面表现更优[21]。

3.3 瑞马唑仑具有轻度术中镇静作用且安全性良好

在本研究中,Remimazolam组椎管内麻醉后15 min OAA/S评分[5(4,5)分],低于Control组的5(5,5)分,其中Remimazolam组评分≤4分者8例(11.4%),提示瑞马唑仑仅产生轻度、一过性的术中镇静作用,30 min后即恢复至与Control组无差异的水平。这一时程特征与瑞马唑仑静脉给药后血药浓度的变化特点一致,Wiltshire等[27]的Ⅰ期临床试验药代动力学-药效学模型显示,瑞马唑仑的镇静效应随血药浓度变化而快速升降,这种超短效、可控性强的药理学特性使其在剖宫产等需要平衡镇静与清醒的医疗场景中具有独特价值。在安全性方面,两组产妇心动过缓、低血压、呼吸困难、恶心、呕吐及头晕等术中不良反应发生率差异均无统计学意义(P>0.05),表明单次静脉注射瑞马唑仑0.2 mg/kg不增加术中不良反应的发生风险。

3.4 研究局限性与展望

本研究为前瞻性随机双盲安慰剂对照试验,旨在验证小剂量瑞马唑仑在CSEA剖宫产中预防寒战的临床疗效与安全性。作为临床转化研究的初始阶段,确立疗效与安全性证据是后续机制探索的前提。尚存在以下局限性:①本研究是单中心研究,未来仍需进行多中心、大样本量的研究验证结果;②主要结局指标均通过主观问诊及问卷调查进行评估,缺乏客观标准化的指标。此外,剖宫产产妇作为特殊人群,伦理委员会明确限制了频繁动脉采血、腰椎穿刺、核心体

温监测等侵入性操作,以保障母婴安全及早期接触。因此,血清递质动态监测、下丘脑电生理研究等深入机制探索在本阶段难以实施,这也是产科麻醉领域临床研究的普遍挑战;③剂量单一,仅采用0.2 mg/kg剂量,未来可探索不同剂量或联合用药方案的效果差异;④仅评估术后90 min内的寒战及术后1~2 d的恢复质量,未追踪长期影响,未来的研究可以延长观察时间,以全面评估其对产妇术后恢复的长期影响。在机制研究层面,后续拟从以下方向深入探索:①中枢与分子机制:参考Muroya等[28]在兔模型中的研究,验证瑞马唑仑是否通过增强下丘脑视前区GABA-A受体活性,升高寒战阈值;并结合Nakamura等[29]关于视前区GABA能神经元体温调节通路的发现,探索其对寒战反射通路的调控作用。②外周与体液机制:检测寒战发生时血清儿茶酚胺、5-羟色胺等体温调节递质动态变化;同步监测核心-外周体温梯度,评估瑞马唑仑是否通过稳定血流动力学、缩小温度梯度间接抑制寒战触发[30]。

综上所述,静脉注射小剂量瑞马唑仑可以降低产妇腰硬联合剖宫产术麻醉后寒战的发生率(*HR*=0.38,95%*CI*:0.22~0.67),具有温和的轻度术中镇静作用,能改善产妇术后恢复质量,并且可能和白细胞和血小板含量有关。但目前直接探讨瑞马唑仑与剖宫产寒战关系的临床研究仍较少,未来需要更多随机对照试验验证其抗寒战效果及剂量-效应关系的研究。

利益冲突 本文所有作者声明不存在利益冲突

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